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EXAMINER	
HIXSON, CHRISTOPHER	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/567,522	NEUEFEIND ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER A. HIXSON	4172	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☒ Claim(s) *23 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *17 Mar 2008 and 11 Dec 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "Method for applying and identifying weakly binding molecule fragments incorporated into protein crystals."

Claim Objections

3. Claims 23 and 24 are objected to because of the following informalities:

- In claim 23, "mixing and applying steps" should be replaced by –fixing and applying steps--.
- In claim 24, "gas stream" does not have antecedent basis in claim 1. For the purpose of the prior art rejection below, it is assumed to instead depend on claim 8, the first mention of a gas stream.

4. Appropriate correction is required.

Double Patenting

5. Claims 1, 4, 7-14, 24, 25, 30, 50 and 51 of this application conflict with claims 36-45, 47, 51-53, and 57-58 of Application No. 10/567193. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence

of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

6. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 1, 4, 7-14, 24-25, 30, and 50-51 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 36-45, 47, 51-53, and 57-58 of copending Application No. 10/567193. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 15, 17, 20, 26, 27, and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 46, 48, 49, and 54-56 of copending Application No. 10/567193. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of each of these claims is only different by minor changes in wording.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-5, 7-10, 13, 14, 24, 25, 29, 32-35, 44, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Rossle et al. ("Fast intercrystalline hydration of beta-chitin revealed by combined microdrop generation and on-line synchrotron radiation microdiffraction" published online Apr. 2003, already of record on Applicant's IDS, hereinafter referred to as Rossele).

12. Regarding claims 1-5, Rossele teaches:

- fixing the crystal on a holding device without being embedded in a liquid environment (p.982, col. 1); and
- applying microdrops of the solution onto the ***protein*** crystal (p.981, col. 1 - p.982, col. 1, where the molecules in the solution are water, a "solution" containing one more more molecule species, which is less than 100 Da).

It is inherent that water binds to the protein. Regarding composition claims, if the composition is the same, it must have the same properties (see MPEP § 2112.01, II.). The affinity with which the ligands bind is not a positively recited limitation, being only preferable.

13. Regarding claims 7-10 and 24, Rossele teaches the limitations of claim 1 as previously described. Rossele further teaches wherein a defined environment is generated around the crystal during the application of microdrops onto the crystal (implicit, because the humidity to the air flow imparted by the streaming droplets creates said defined environment, see p.981, "Microdrop generation" and "X-ray Diffraction Setup", for description of the environment created in the prior art method). The gas stream has a defined composition because the humidity is due solely to the water vapor, which means that the air humidity is controlled. That the gas stream is regulated by during the drip-on procedure is implied because in this reference, the drip-on procedure is *due* to the drip-on procedure. Additionally, the gas stream contains at least one substance, water, which can act as a ligand for protein binding.

14. Regarding claims 13 and 14, Rossele teaches the limitations of claim 1 as previously described. Rossele further teaches wherein the microdrops have a volume

of 65 pL (p.981, col. 1). This means that the drops are smaller than the volume of the crystal (not least because claim 14 which depends on claim 13 recites the range 4 pL - 1 nL), and the size of the droplets anticipates the range of 4 pL - 1 nL recited in claim 14.

15. Regarding claim 25, Rossele teaches the steps of claim 1 (part (a) of the instant claim) as previously described. Rossele further teaches:

- (b) irradiating the crystal with X-ray or synchrotron radiation (p.981, col. 2), and
- (c) recording the diffraction image of the crystal (p.981, col. 2).

16. Regarding claim 29, Rossele teaches the limitations of claim 25 as previously described. Rossele further teaches wherein the irradiation is conducted with monochromatic X-ray radiation (p.981, col. 2) or with synchrotron radiation during the treatment of the crystals with the solution (p.984, col. 1).

17. Regarding claim 32, Rossele teaches the limitations of claim 1 as previously described. Rossele further teaches wherein the method is conducted with a device for treating a crystal with a substance having a holder (p.982, col. 1) for fixing the crystal and at least one micro dosage system (p. 981, col. 1, "Microdrop generation"), which is arranged in relation to the holder in such a way that it can apply microdrops of the liquid onto the crystal fixed in the holder (Fig. 1).

18. Regarding claims 33-35, Rossele teaches the limitations of claim 32 as previously described. Rossele further teaches wherein a defined environment is generated around the crystal during the application of microdrops onto the crystal

(implicit, because the humidity to the air flow imparted by the streaming droplets creates said defined environment). The gas stream has a defined composition because the humidity is due solely to the water vapor, which means that the air humidity is controlled. The holder is developed in such a way that the gas stream can be lead through the holder in such a way that it is directed toward the crystal fixed in the holder (Fig. 1, where gas stream flows from dispensing head).

19. Regarding claims 44 and 45, Rossele teaches the limitations of claim 32 as previously described. Rossele further teaches wherein the microdrops have a volume of 65 pL (p.981, col. 1). This means that the drops are smaller than the volume of the crystal (not least because claim 14 which depends on claim 13 recites the range 4 pL - 1 nL). This makes the drops inherently having a volume between 5%-20% of the crystal's volume, as a typical protein crystal's volume is measured in microliters.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Hasnain et al. ("Structure of metal centres in proteins at subatomic resolution" 1999, hereinafter referred to as Hasnain).

23. Regarding claim 6, Rossele teaches the limitations of claim 1 as previously described. However, Rossele does not teach wherein the molecules contained in the solution or the molecules of at least one molecule species contained in the solution have at least one electron-rich or anomalous dispersion center, preferably a heavy metal atom.

24. In the same field of endeavor of X-ray crystallographic analysis of proteins, Hasnain teaches wherein lanthanides when incorporated into protein complexes are used to aid in determining the crystal structure of the protein (p.858, col. 2) for the benefit of solving the phase problem in protein crystallography.

25. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the molecules contained in the solution or the molecules of at least one molecule species contained in the solution have at least one electron-rich or anomalous dispersion center, preferably a heavy metal atom in order to solve the phase problem in protein crystallography.

26. Claims 11, 12, 15, 16, 18, 19, 36-43, and 46-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Kiefersauer et al. ("A novel free-mounting system for protein crystals: transformation and improvement of diffraction

power by accurately controlled humidity changes" 2000, hereinafter referred to as Kiefersauer).

27. Regarding claim 11, Rossele teaches the limitations of claim 9 as previously described. However, Rossele does not teach wherein the air humidity of the gas stream and the frequency, at which the drops are dripped onto the crystal by means of the micro-dosage system, are synchronized during the drip-on procedure in such a way that the crystal is strained as little as possible and, in particular, that the volume of the crystal alters by no more than 20%, in particular by no more than 10%.

28. In the same field of endeavor of protein crystallography, Kiefersauer teaches that the humidity and temperature of the gas stream can be regulated by computer to achieve desirable effects on the protein crystal (p.1224, col. 1) for the benefit of ensuring that the crystal is in a suitable state for the planned experiments. One of ordinary skill in the art would have understood, and would have anticipated as predictably successful, to simultaneously control the microdroplets taught by Rossele with the humidity and temperature controls taught by Kiefersauer because said drops are also affected by the humidity and temperature of the gas stream. Additionally, Kiefersauer teaches that it is possible to control the humidity of the gas stream such that an intentional shrinkage of 17% can be induced (p.1227, col. 1). Thus, controlling the gas stream to minimize disruptions in the volume of the crystal is within the ambit on one of ordinary skill in the art.

29. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the air humidity of the gas stream and

the frequency, at which the drops are dripped onto the crystal by means of the micro-dosage system, are synchronized during the drip-on procedure in such a way that the crystal is strained as little as possible and, in particular, that the volume of the crystal alters by no more than 20%, in particular by no more than 10% in order to ensure that the crystal is in a suitable state for the planned experiments.

30. Regarding claims 12, Rossele teaches the limitations of claim 8 as previously described. However, Rossele does not teach wherein the gas stream comprises a solubilizer at a controlled concentration for a substance to be applied onto the crystal.

31. In the same field of endeavor of protein crystallography, Kiefersauer teaches that a saturated (controlled concentration) methanol or formaldehyde vapor (solubilizer) is applied to the crystal (p.1227, col. 1, 3.2.2, "Special gases") for the benefit of applying these substances in a manner that does not destroy the crystal under study. Rather than applying these solvents via the gas phase, it would have been obvious to try applying them in the form of microdroplets, as Rossele teaches to do to hydrate a crystal.

32. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the gas stream comprises a solubilizer at a controlled concentration for a substance to be applied onto the crystal in order to apply these substances in a manner that does not destroy the crystal under study.

33. Regarding claims 15, 16, 18, and 19, Rossele teaches the limitations of claim 1 as previously described. However, Rossele does not teach wherein the solution containing the molecule species and applied onto the crystal is an aqueous solution or a

solution, at least partially, comprising organic solvents, and, optionally, being heated up to more than 20°C.

34. In the same field of endeavor of protein crystallography, Kiefersauer teaches that humid air and methanol are applied onto the crystal (p.1227, col. 1, 3.2.2, "Special gases"). Additionally, Kiefersauer teaches that the temperature of the gas stream should be a few degrees above room temperature (ie above 20°C). Rather than applying these solvents via the gas phase, it would have been obvious to try applying them in the form of microdroplets, as Rossele teaches to do to hydrate a crystal for the benefit of preparing the crystal in a state suitable for the intended analysis.

35. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the solution containing the molecule species and applied onto the crystal is an aqueous solution or a solution, at least partially, comprising organic solvents, and, optionally, being heated up to more than 20°C, contains a volatile organic solvent which boils at a temperature below 100°C, and contains methanol in order to prepare the crystal in a state suitable for the intended analysis.

36. Regarding claims 36-38, Rossele teaches the limitations of claim 1 as previously described. However, Rossele does not teach wherein the method uses a device having a holder consisting of a carrier block for a holder capillary, which has a free support end for the crystal, is used, where said holder capillary is a micropipette in which a negative pressure can be generated in order to hold the crystal, and where the carrier block of

the holder of the device has an integrated gas channel having a mouth end, which is directed toward the support end of the holder capillary.

37. In the same field of endeavor of protein crystallography, Kiefersauer teaches wherein the method uses a device having a holder consisting of a carrier block (Fig. 2, "insert") for a holder capillary ("micropipette", Fig. 2, attached to a vacuum line), which has a free support end for the crystal, is used, and where the carrier block of the holder of the device has an integrated gas channel having a mouth end, which is directed toward the support end of the holder capillary (Fig. 2., where the gas channel is described in the caption) for the benefit of providing a structure on which the crystal can be mounted.

38. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the method uses a device having a holder consisting of a carrier block for a holder capillary, which has a free support end for the crystal, is used, where said holder capillary is a micropipette in which a negative pressure can be generated in order to hold the crystal, and where the carrier block of the holder of the device has an integrated gas channel having a mouth end, which is directed toward the support end of the holder capillary in order to provide a structure on which the crystal can be mounted.

39. Regarding claims 39 and 40, Rossele teaches the limitations of claim 34 as previously described. However, Rossele does not teach wherein a device is used, which has a gas mixing device, capable of variably adjusting the composition of the gas

stream, and wherein the gas consists of air having a specific humidity content and the gas mixing device is capable of adjusting the air humidity.

40. In the same field of endeavor of protein crystallography, Kiefersauer teaches wherein a device is used, which has a gas mixing device, capable of variably adjusting the composition of the gas stream, and wherein the gas consists of air having a specific humidity content and the gas mixing device is capable of adjusting the air humidity (p.1223 col. 2 - p.1224, col. 1) for the benefit of maintaining the crystal in conditions suitable for the intended experiment.

41. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein a device is used, which has a gas mixing device, capable of variably adjusting the composition of the gas stream, and wherein the gas consists of air having a specific humidity content and the gas mixing device is capable of adjusting the air humidity in order to maintain the crystal in conditions suitable for the intended experiment.

42. Regarding claims 41 and 42, Rossele teaches the limitations of claim 34 as previously described. However, Rossele does not teach wherein a device is used which comprises a device for adding a solubilizer capable of adding to the gas stream a solubilizer for a substance to be introduced into the crystal structure of the crystals, and which further comprises a concentration adjusting device for adjusting the concentration of the solubilizer.

43. In the same field of endeavor of protein crystallography, Kiefersauer teaches wherein a device is used which comprises a device for adding a solubilizer capable of

adding to the gas stream a solubilizer for a substance to be introduced into the crystal structure of the crystals (p.1227, col. 1 "3.2.2 Special gases"), and which further comprises a concentration adjusting device for adjusting the concentration of the solubilizer (p.1227, col. 1 "3.2.2 Special gases", "regulated by a valve") for the benefit of preparing the crystal in a manner suitable for the intended experiment.

44. Regarding claim 43, Rossele teaches the limitations of claim 34 as previously described. However, Rossele does not teach wherein a device is used which comprises a temperature regulating device capable of variably adjusting the temperature of the gas stream.

45. In the same field of endeavor of protein crystallography, Kiefersauer teaches wherein a device is used which comprises a temperature regulating device capable of variably adjusting the temperature of the gas stream (p.1224, col. 2, "heating element and temperature sensor") for the benefit of preparing the crystal in a manner suitable for the intended experiment.

46. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to perform the method wherein a device is used which comprises a temperature regulating device capable of variably adjusting the temperature of the gas stream in order to prepare the crystal in a manner suitable for the intended experiment.

47. Regarding claim 46, Rossele in view of Kiefersauer stands as applied to claim 42. Rossele further teaches wherein the microdrops have a volume of 65 pL (p.981, col. 1).

48. Regarding claims 47-49, Rossele teaches the limitations of claim 1 as previously described. Rossele further teaches wherein a device is used in which the microdosage system is developped in such a way that it comprises a piezo pipette (p.981, "Microdrop generation") which can be generated in time-controled manner (p.981, col. 2, controlled by software).

49. However, Rossele does not teach wherein the system is capable of supplying different liquids or that it is electrically controllable with electrically controllable valves with different liquid supply containers.

50. In the same field of endeavor of protein crystallography, Kiefersauer teaches wherein water and methanol are required to prepare the crystal for the intended experiment (p.1227, "3.2.2 Special gases") in the same stream. Consequently, one of ordinary skill in the art would have understood to design the system such that it could deliver said species in the manner described in the instant claims.

51. Thus it would have been obvious to one of ordinary skill in the art to have performed the method wherein the system is capable of supplying different liquids or that it is electrically controllable with electrically controllable valves with different liquid supply containers in order to prepare the crystal for the intended experiment.

52. Regarding claim 50, Rossele teaches the limitations of claim 1 as previously described. However, Rossele does not teach wherein the crystal is vapor-plated with solvent, in particular with organic solvent, by means of an evaporator.

53. In the same field of endeavor of protein crystallography, Kiefersauer teaches wherein the crystal is vapor-plated with solvent, in particular with organic solvent, by

means of an evaporator (p.1227, "3.2.2 Special gases") for the benefit of introducing a ligand in a non-destructive manner.

54. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the crystal is vapor-plated with solvent, in particular with organic solvent, by means of an evaporator in order to introduce a ligand in a non-destructive manner.

55. Regarding claim 51, Rossele teaches:

- (a) holding one or more crystals ready (p.982, col. 1),
- (b) applying microdrops of a solution containing at least one ligand onto the preferably freely mounted crystals (p.981, col. 1 - p.982, col. 1, where the molecules in the solution are water, a "solution" which is a ligand which binds to proteins), and
- (d) examining the crystals X-ray crystallographically (p.981, col. 2—p.982, col. 1).

However, Rossele does not teach (c) storing the crystals treated according to the step (b).

56. In the same field of endeavor of protein crystallography, Kiefersauer teaches storing the crystals treated according to the step (b) (p.1227, col. 2, paragraph 2-3) for the benefit of maintaining the crystal for study after it has been prepared.

57. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have stored the crystals treated according to the step (b) in order to maintain the crystal for study after it has been prepared.

58. Claims 17 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Kiefersauer in further view of Nienaber et al. ("Discovering novel ligands for macromolecules using X-ray crystallographic screening" 2000, already of record on applicant's IDS, hereinafter referred to as Nienaber).

59. Regarding claim 17, Rossele in view of Kiefersauer stands as applied to claim 16. However, the prior art combination does not teach wherein the solvent consists of or contains DMSO.

60. In the same field of endeavor of crystallographic screening for drug discovery, Nienaber teaches wherein DMSO is used to dissolve fragments intended for use in drug discovery applications by soaking a protein crystal followed by subsequent X-ray analysis ("Experimental protocol", p.1107). Combined with the teachings used to reject claim 16 above in paragraph 22 of this document, one of ordinary skill in the art would have predicted a reasonable chance of success of performing the analysis described by Nienaber using a humidified droplet application scheme, because both Rossele and Kiefersauer indicate methods than can be used to incorporate molecules of interest (water or methanol, for example) into a protein crystal using vapor and/or microdroplets for the benefit of preparing the crystal in a state suitable for the intended analysis.

61. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the solvent consists of or contains DMSO in order to prepare the crystal in a state suitable for the intended analysis.

62. Regarding claims 20-22, Rossele teaches the limitations of claim 1 as previously described. However, Roselle does not teach wherein the molecules contained in the

solution to be applied onto the crystal are hardly water-soluble, where the solution contains a cocktail of at least 3 different molecule species, and wherein the solution contains at least one molecule species at a concentration of 0.001 - 0.1 M.

63. In the same field of endeavor of protein crystallography, Kiefersauer teaches that soaking crystals destroys the crystals, even when supplied with a low concentration of methanol (p.1227, "3.2.2 Special gases"). Thus one of ordinary skill would have been motivated to introduce compounds intended to be incorporated into a crystal by means other than soaking. Combined with the teaching of Rossele, indicating that water droplets become incorporated into protein crystals, one of ordinary skill in the art would have predicted a reasonable chance of success of incorporating species dissolved in droplets in to a protein crystal for the benefit of preparing the crystal in a manner suitable for the intended experiment, and that this approach would have been preferable to soaking, which as taught by Kiefersauer is prone to damaging the crystal.

64. Thus it would have been obvious to spray droplets of a solvent containing dissolved species as a way in incorporating said species into the protein crystal in order to prepare the crystal in a manner suitable for the intended experimentation.

65. However, the prior art combination does not teach wherein the molecules contained in the solution to be applied onto the crystal are hardly water-soluble, where the solution contains a cocktail of at least 3 different molecule species, and wherein the solution contains at least one molecule species at a concentration of 0.001 - 0.1 M.

66. In the same field of endeavor of studying binding sites with crystallography, Nienaber teaches wherein a protein crystal is soaked in a DMSO solution containing 6-8

different species at a concentration of about 0.1 M (p.1107, "Experimental details," col .2) for the benefit of preparing the crystal in a state suitable for the intended analysis. These species are soluble in DMSO, but as listed on p.1106, col. 2, are sparingly soluble in water.

67. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the molecules contained in the solution to be applied onto the crystal are hardly water-soluble, where the solution contains a cocktail of at least 3 different molecule species, and wherein the solution contains at least one molecule species at a concentration of 0.001 - 0.1 M in order to prepare the crystal in a state suitable for the intended analysis.

68. Claims 23 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Erlanson et al. ("Fragment-based drug discovery" Jun 2004, hereinafter referred to as Erlanson).

69. Regarding claims 23 and 52, Rossele teaches the limitations of claim 1 as previously described. However, Rossele does not teach the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method.

70. In the same field of endeavor of the study of proteins using spectroscopy and crystallography, Erlanson teaches that NMR can be used to screen ligands for binding affinity to a protein (p.3465) for the benefit of selecting interesting fragments for study. This step is especially considered a preliminary step because crystallography is

generally considered a more arduous technique (p.3466, col. 2, "2.4 Crystallography-based approaches").

71. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method including the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method, such as NMR, in order to select interesting fragments for study.

72. Claims 23 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Huth et al. ("Utility of NMR in lead optimization: Fragment-based approaches" 2002, hereinafter referred to as Huth).

73. Regarding claims 23 and 52, Rossele teaches the limitations of claim 1 as previously described. However, Rossele does not teach the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method for the benefit of selecting interesting fragments to study.

74. In the same field of endeavor of the study of proteins using spectroscopy and crystallography, Huth teaches that NMR can be used to screen ligands for binding affinity to a protein (abstract) for the benefit of selecting interesting fragments for study.

75. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method including the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method, such as NMR, in order to select interesting fragments for study.

76. Claims 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Nienaber.

77. Regarding claim 26, Rossele teaches the limitations of claim 25 as previously described. However, Rossele does not teach wherein the method further comprises calculating an electron density map using the phase information and the intensity of the reflexes in the diffraction image and determining the binding site and positioning of the at least one bound molecule species.

78. In the same field of endeavor of studying binding sites with crystallography, Nienaber teaches wherein the method further comprises calculating an electron density map using the phase information and the intensity of the reflexes in the diffraction image (p.1107, "Experimental protocol") and determining the binding site and positioning of the at least one bound molecule species (p.1106, col. 2) for the benefit of solving the crystal structure.

79. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method such that it further comprises calculating an electron density map using the phase information and the intensity of the reflexes in the diffraction image and determining the binding site and positioning of the at least one bound molecule species in order to solve the crystal structure.

80. Regarding claim 28, Rossele in view of Nienaber stands as applied to claim 26. However, the prior art combination does not teach wherein the binding site and positioning of the at least one bound molecule species in the structure is determined from the difference of electron densities of non-complexed and complexed structure by means of an electron density difference map.

81. Nienaber further teaches to measure the electron density before and after complexation (Fig. 1 and Fig. 2), indicating the position of the bound species. Consequently, one of ordinary skill in the art would have appreciated a reasonable chance of successfully determining the binding site and positioning of the molecule species by taking the difference of the electron densities of the before and after complexation structures for the benefit of simplifying the data to be analyzed.

82. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method such that the binding site and positioning of the at least one bound molecule species in the structure is determined from the difference of electron densities of non-complexed and complexed structure by means of an electron density difference map in order to simplify the data to be analyzed.

83. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Nienaber in further view of Hasnain.

84. Regarding claim 27, Rossele in view of Nienaber stands as applied to claim 26. However the prior art combination does not teach wherein the phase information is obtained using heavy metal atom derivatives, "molecular replacement", or MAD.

85. In the same field of endeavor of solving protein crystal structures, Hasnain teaches to obtain phase information using MAD (p.858, "4.2 Early experiments and their impact on MAD") for the benefit of solving the phase problem in protein crystallography.

86. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to perform the method wherein the phase information is obtained using heavy

metal atom derivatives, "molecular replacement", or MAD in order to solve the phase problem.

87. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Kiefersauer in further view of Nienaber in still further view of Erlanson.

88. In the same field of endeavor of protein crystallography, Kiefersauer teaches that soaking crystals destroys the crystals, even when supplied with a low concentration of methanol (p.1227, "3.2.2 Special gases"). Thus one of ordinary skill would have been motivated to introduce compounds intended to be incorporated into a crystal by means other than soaking. Combined with the teaching of Rossele, indicating that water droplets become incorporated into protein crystals, one of ordinary skill in the art would have predicted a reasonable chance of success of incorporating species dissolved in droplets in to a protein crystal for the benefit of preparing the crystal in a manner suitable for the intended experiment, and that this approach would have been preferable to soaking, which as taught by Kiefersauer is prone to damaging the crystal.

89. Thus it would have been obvious to spray droplets of a solvent containing dissolved species as a way in incorporating said species into the protein crystal in order to prepare the crystal in a manner suitable for the intended experimentation.

90. However, the prior art combination does not teach wherein fragments are incorporated into the crystal.

91. In the same field of endeavor of protein crystallography, Nienaber teaches to soak a crystal with fragments to determine binding. It further teaches determining the

structure of at least one complex having at a fragment bound (p.1106, col. 2) for the benefit of determining candidates for inhibitors.

92. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of at least one complex having a fragment bound in order to determine candidates for inhibitors.

93. However, the prior art combination does not teach wherein the structure of one complex having at least two fragments is determined, where linkers are determined, and the synthesis of the ligand containing the two fragments and the linker is performed.

94. In the same field of endeavor of drug discovery, Erlanson teaches determining the structure of one complex having at least two fragments, determining a linker, and synthesizing the final ligand (p.3467, col. 1, first paragraph) for the benefit of developing a drug candidate.

95. This it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of one complex having at least two fragments, determining a linker, and synthesizing a final ligand in order to develop a drug candidate.

96. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele in view of Kiefersauer in further view of Nienaber in still further view of Huth.

97. In the same field of endeavor of protein crystallography, Kiefersauer teaches that soaking crystals destroys the crystals, even when supplied with a low concentration of methanol (p.1227, "3.2.2 Special gases"). Thus one of ordinary skill would have been motivated to introduce compounds intended to be incorporated into a crystal by means

other than soaking. Combined with the teaching of Rossele, indicating that water droplets become incorporated into protein crystals, one of ordinary skill in the art would have predicted a reasonable chance of success of incorporating species dissolved in droplets in to a protein crystal for the benefit of preparing the crystal in a manner suitable for the intended experiment, and that this approach would have been preferable to soaking, which as taught by Kiefersauer is prone to damaging the crystal.

98. Thus it would have been obvious to spray droplets of a solvent containing dissolved species as a way in incorporating said species into the protein crystal in order to prepare the crystal in a manner suitable for the intended experimentation.

99. However, the prior art combination does not teach wherein fragments are incorporated into the crystal.

100. In the same field of endeavor of protein crystallography, Nienaber teaches to soak a crystal with fragments to determine binding. It further teaches determining the structure of at least one complex having at a fragment bound (p.1106, col. 2) for the benefit of determining candidates for inhibitors.

101. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of at least one complex having a fragment bound in order to determine candidates for inhibitors.

102. However, the prior art combination does not teach wherein the structure of one complex having at least two fragments is determined, where linkers are determined, and the synthesis of the ligand containing the two fragments and the linker is performed.

103. In the same field of endeavor of drug discovery, Huth teaches determining the structure of one complex having at least two fragments, determining a linker, and synthesizing the final ligand (Fig. 1) for the benefit of developing a drug candidate.

104. This it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of one complex having at least two fragments, determining a linker, and synthesizing a final ligand in order to develop a drug candidate.

105. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossele.

106. Regarding claim 30, Rossele teaches the limitations of claim 1 as previously described. Rossele further teaches wherein at least one molecule is applied, diffraction intensities are measured as a function of time, and said intensities are compared with respect to their time-dependent sequence (see p.981, "X-ray diffraction setup", and Fig. 4).

107. However, Rossele does not teach wherein the intensities are measured at intervals with a variable length. As long as the intervals are small enough to capture the physics of interest, the length of the interval does not affect the result. Consequently, one of ordinary skill in the art would appreciate that said interval could obviously be allowed to be of variable length for the benefit of optimally capturing data of interest.

108. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method such that the intensities are measured at intervals with a variable length in order to optimally capture the data of interest.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER A. HIXSON whose telephone number is (571)270-5027. The examiner can normally be reached on M-F 7:30 AM EST - 5:00 PM EST, alt Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Angela Ortiz can be reached on (571)272-1206. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Cah

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